Monoclonal gammopathy associated membranous glomerulonephritis: A rare entity

K. K. Gowda, K. Joshi, R. Ramachandran[1], R. Nada

Departments of Histopathology and [1]Nephrology, PGIMER, Chandigarh, India

ABSTRACT

A 40-year-old male presented with nephrotic syndrome. Light microscopic analysis of the renal biopsy showed thickening of the glomerular capillary wall. Immunofluorescence examination revealed granular deposition of monoclonal immunoglobulin (Ig) G3-kappa and complement C3 along the glomerular basement membrane. Electron microscopy showed subepithelial electron dense deposits, thus confirming membranous glomerulonephritis (MGN) with monoclonal gammopathy. MGN with monoclonal gammopathy is an extremely rare but distinctive entity. This patient was treated with a combination of bortezomib, thalidomide and dexamethasone and showed partial remission of his nephrotic state and dysproteinemia.

Key words: Membranous glomerulonephritis, monoclonal gammopathy, immunoglobulin

Introduction

Membranous glomerulonephritis (MGN) is a common cause of nephrotic syndrome in adults. The characteristic immunofluorescence finding is granular staining for polyclonal immunoglobulin (Ig) and complements along glomerular basement membranes.[1] Monoclonal gammopathy associated MGN is rare and distinct entity and only 13 cases have been reported so far. However, its natural history and clinical features are yet to be ascertained. Here we describe a case of monoclonal IgG3-kappa deposition associated with pure membranous morphology.

Case Report

A 40-year-old male presented with facial puffiness and edema of lower extremities of 7 months duration. He had no history of bony pain, oral ulcers, arthralgia, skin rashes or any features suggestive of connective tissue disorder. On examination patient had pitting edema of lower limbs with no pallor, icterus or skin rashes. Blood pressure was 110/70 mm Hg. Systemic examination was normal. Urine microscopic examination revealed 4 + proteinuria with no active sediments. Twenty-four hours urine protein was 6.9 g. Renal function tests revealed blood urea nitrogen of 25 and serum creatinine of 2.06 mg/dl respectively. Patient had hemoglobin of 138 g/L, total leucocyte count of 11×10^9/L with normal differential counts and platelet count of 3.4 lakhs/micro litre. Serum total protein and albumin were 5.5 and 2.5 g/dl respectively. Liver function tests were normal. Patient's serum tested negative for hepatitis B surface antigen, antibodies for hepatitis C virus and human immunodeficiency virus-I/II. Antinuclear factor, rheumatoid factor, cryoglobulin and antineutrophil cytoplasmic antibodies were negative and serum complement levels were normal (C3 = 110 mg/dl and C4 = 20 mg/dl). Serum total cholesterol and triglyceride were 352 and 328 mg/dl. Ultrasonography revealed normal sized kidneys. With clinical diagnosis of nephrotic syndrome, ultrasound guided percutaneous kidney biopsy was performed.

Light microscopic examination showed eight glomeruli, all showed diffuse thickening of glomerular capillary walls with lifting up of podocytes. Jones silver stain revealed spikes [Figure 1]. No endocapillary or mesangial proliferative, tubulointerstitial and vascular alterations were noted. Immunofluorescence showed granular

Address for correspondence:
Dr. Ritambhra Nada,
Department of Histopathology, PGIMER, Chandigarh, India.
E-mail: ritamduseja@yahoo.com

Access this article online	
Quick Response Code:	Website: www.indianjnephrol.org
	DOI: 10.4103/0971-4065.135353

polyclonal IgG, kappa light chain and deposition of monoclonal IgG3 and C3 along glomerular capillary loops with intensity being 3 + on a scale of 0-3+ [Figure 2]. IgA, IgM, lambda light chain and complement (C1q) were negative. No deposition along tubular basement membranes was observed. Therefore, a diagnosis of MGN with monoclonal IgG3-kappa deposition was made on renal biopsy.

Urine and serum immunoelectrophoresis showed no monoclonal proteins. Serum kappa and lambda light chain concentrations were 1088 and 208 mg/dl respectively with κ/λ ratio of 5.2 (normal - 0.26-1.52). Skeletal survey did not reveal any abnormalities. Bone marrow examination revealed 3% plasma cells. With a diagnosis of monoclonal gammopathy with MGN, patient was started on treatment with 6 monthly cycles of velcade-thalidomide-dexamethasone (VTD) regimen (bortezomib - 1.3 mg/m^2 on 1st, 4th, 7th and 11th days, thalidomide - 200 mg/day and dexamethasone - 30 mg/kg on 1st-4th and 7th-11th days of month). After 6 monthly cycles of VTD therapy, patient had reduction in proteinuria to 3.1 g/day with serum creatinine and albumin of 0.9 mg/dl and 3.1 g/dl respectively. Repeat serum free light assay revealed kappa and lambda light chain of 29 and 14 mg/dl respectively (κ/λ ratio: 2.01).

Discussion

Membranous glomerulonephritis is the commonest cause of nephrotic syndrome in adults. The changes in glomerular basement membrane by light and electron microscopy are due to deposits of Ig and complement components and reactive changes in glomerular basement membrane. The principal immune reactant in these deposits is IgG. Among IgG subclasses, IgG4 is the predominant Ig with IgG1 and IgG3 being less commonly seen in idiopathic MGN.[2,3] However, studies conducted could not determine whether IgG subclass imbalance was due to clonally restricted antibody response to particular antigen or to host immune response defect or both.[4] Although MGN cases show preponderance of IgG4, they do not exhibit monoclonality.

In our case report, we describe MGN with monoclonal IgG3 with kappa restriction, which is not characteristic finding of idiopathic MGN. Till date only 13 cases of pure membranous morphology with monoclonal gammopathy have been described in literature.[5-10] This is the fourteenth such case being reported.

The first report of MGN with monoclonal deposits[5] was described in the autopsy examination of kidneys from a 81-year-old woman with follicular B-cell lymphoma with nephrotic syndrome who died of pulmonary thromboembolism. Histology, IF and elution studies revealed subepithelial granular IgG1-κ deposits. Subsequently various authors have described such cases[6-10] of pure membranous morphology with monoclonal deposits, with largest series being by Guiard *et al*. (six cases).

Complete data amongst these 13 cases, is available in eight, with age range of 24-81 years [Table 1] with majority being males (6/8). All patients had proteinuria with 5/8 developing nephrotic syndrome. Renal insufficiency was not observed in any of the cases. Ten cases showed κ restriction, while IgG3 was the most common Ig subclass (five cases). Our case had nephrotic

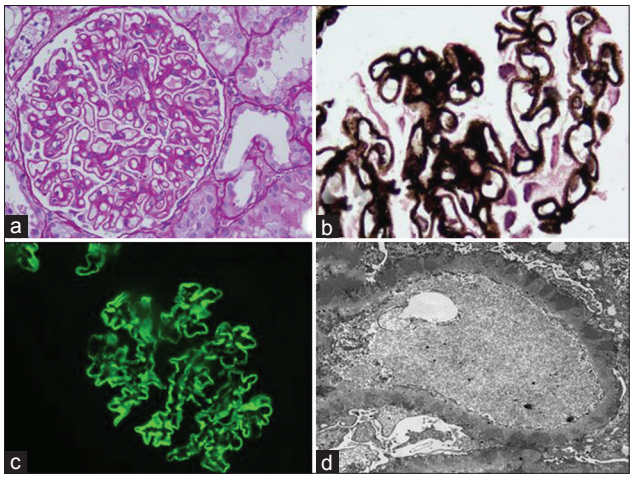

Figure 1: A glomerulus with thickened glomerular capillary loops (a, PAS stain; ×400) and spikes on Jones stain (arrow in b, ×400). Immunoflourescence shows immunoglobulin G deposits (c), which on electron microscopy were subepithelial in location (d)

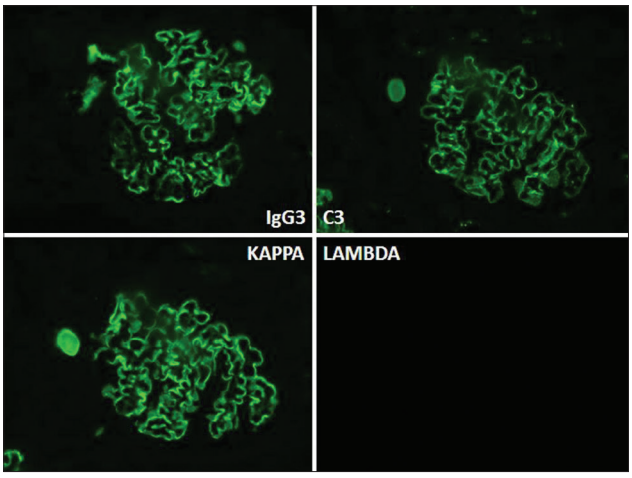

Figure 2: Immunoflourescence study showing granular deposits of immunoglobulin (Ig) G3, C3 and Kappa along the glomerular capillary loops, while lambda is negative. Immunoflourescence for IgG1, IgG2 and IgG4 were negative

Table 1: Cases with membranous glomerulonephritis associated with monoclonal deposits in the glomeruli

Authors	Cases	Age/gender	Proteinuria (g/day)	IF#	EM*	Dysproteinemia
Evans *et al.*[5]	1	81/female	NS$	IgG1 κ	SEμ	BJP∞+
Komatsuda *et al.*[6]	2	44/male	1.7	IgG3 κ	SE	-
	3	42/male	5.6	IgG1 κ	SE	-
	4	24/male	1.9	IgG3 κ	SE	-
Sophie *et al.*[7]	5	62/female	3.9	IgG1 λ	SE	SPEP£
Miura *et al.*[8]	6	61/male	1.1	IgA1 λ	SE	-
Guiard *et al.*[9]	7 (case 16)	-	-	IgG1 κ	SE	-
	8 (case 18)	-	-	IgG1 λ	SE	SPEP
	9 (case 19)	-	-	IgG1 κ	SE	-
	10 (case 20)	-	-	IgG3 κ	SE	-
	11 (case 25)	-	-	IgG2 κ	SE	-
	12 (case 26)	-	-	IgG3 κ	SE	-
Yamada *et al.*[10]	13	63/male	16	IgG1 λ	SE	-
Our case	14	40/male	6.9	IgG3 κ	SE	↑κ>λ ratio

#Immunoflourescence, $Nephrotic syndrome, ∞Bence Jones protein, *Electron microscopy, μSubepithelial deposit, £Serum protein electrophoresis, ↑-Increased

syndrome without renal insufficiency and showed kappa restricted IgG3 deposition. It is interesting to note that none of these cases showed IgG4 deposition unlike idiopathic MGN.[3]

All cases showed nonorganized immune complex type subepithelial deposits on electron microscopy, in contrast to punctate deposits seen in Randall type of monoclonal Ig deposition disease.[11] One of the explanations given by Sophie *et al*.[7] for the subepithelial deposits was that, *in vivo* precipitation is facilitated by the local concentration of protein in glomerular basement membrane and ionic properties of negatively charged local milieu. This was based on their observation of unusual biochemical properties of precipitating IgG in their patient on exposure of serum to low salt concentration. They hypothesized that in contrast to classic membranous nephropathy,[12] deposited Ig probably is not directed against a local antigen, but rather precipitates because of peculiar physicochemical properties. Other more plausible explanation can be that, monoclonal antibodies are directed against particular antigen either in podocyte or glomerular basement membrane similar to antibodies against PLA2R in primary MGN, seen in 60-80% primary MGN.[12] This view is supported by Debiec *et al*. who described a case of recurrent MGN in both native and allograft kidneys caused by IgG3k targeting PLA2 receptor.[13]

Only 4 (including our case) have shown dysproteinemia (altered κ:λ ratio). The inability to identify corresponding monoclonal protein may relate to its presence at very low titers, below the level of detection by standard immunoelectrophoresis, or to rapid rates of tissue deposition. Overt B-cell neoplasm was present in three cases (1 - follicular lymphoma, 1 - multiple myeloma, 1 - chronic lymphocytic leukemia). Most of these patients responded well to steroids. Our patient is first case to be treated with VTD regimen. The patient has achieved partial remission with decline in serum light chain levels and proteinuria 6 months post therapy. He is on close follow-up to look for evidence of plasma cell dyscrasia.

Conclusion

We have described the fourteenth case of monoclonal gammopathy associated with MGN, who was treated with VTD therapy for the first time and showed a partial response.

References

1. Nachman PH, Jennette JC, Falk RJ. Membranous glomerulopathy. In: Brenner BM, editor. Brenner and Rector's the Kidney. Philadelphia, US: Saunders; 2004. p. 1007-14.
2. Imai H, Hamai K, Komatsuda A, Ohtani H, Miura AB. IgG subclasses in patients with membranoproliferative glomerulonephritis, membranous nephropathy, and lupus nephritis. Kidney Int 1997;51:270-6.
3. Kuroki A, Iyoda M, Shibata T, Sugisaki T. Th2 cytokines increase and stimulate B cells to produce IgG4 in idiopathic membranous nephropathy. Kidney Int 2005;68:302-10.
4. Noël LH, Aucouturier P, Monteiro RC, Preud'Homme JL, Lesavre P. Glomerular and serum immunoglobulin G subclasses in membranous nephropathy and anti-glomerular basement membrane nephritis. Clin Immunol Immunopathol 1988;46:186-94.
5. Evans DJ, Macanovic M, Dunn MJ, Pusey CD. Membranous glomerulonephritis associated with follicular B-cell lymphoma and subepithelial deposition of IgG1-kappa paraprotein. Nephron Clin Pract 2003;93:c112-8.
6. Komatsuda A, Masai R, Ohtani H, Togashi M, Maki N, Sawada K, *et al.* Monoclonal immunoglobulin deposition disease associated with membranous features. Nephrol Dial Transplant 2008;23:3888-94.
7. de Seigneux S, Bindi P, Debiec H, Alyanakian MA, Aymard B, Callard P, *et al.* Immunoglobulin deposition disease with a membranous pattern and a circulating monoclonal immunoglobulin G with charge-dependent aggregation properties. Am J Kidney Dis 2010;56:117-21.
8. Miura N, Uemura Y, Suzuki N, Suga N, Maeda K, Yamaguchi S, *et al.* An IgA1-lambda-type monoclonal immunoglobulin deposition disease associated with membranous features in a patient with

chronic hepatitis C viral infection and rectal cancer. Clin Exp Nephrol 2010;14:90-3.
9. Guiard E, Karras A, Plaisier E, Duong Van Huyen JP, Fakhouri F, Rougier JP, *et al.* Patterns of noncryoglobulinemic glomerulonephritis with monoclonal Ig deposits: Correlation with IgG subclass and response to rituximab. Clin J Am Soc Nephrol 2011;6:1609-16.
10. Yamada T, Arakawa Y, Mii A, Kashiwagi T, Kaneko T, Utsumi K, *et al.* A case of monoclonal immunoglobulin G1-lambda deposition associated with membranous feature in a patient with hepatitis C viral infection. Clin Exp Nephrol 2012;16:468-72.
11. Lin J, Markowitz GS, Valeri AM, Kambham N, Sherman WH, Appel GB, *et al.* Renal monoclonal immunoglobulin deposition disease: The disease spectrum. J Am Soc Nephrol 2001;12:1482-92.
12. Beck LH Jr, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, *et al.* M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 2009;361:11-21.
13. Debiec H, Hanoy M, Francois A, Guerrot D, Ferlicot S, Johanet C, *et al.* Recurrent membranous nephropathy in an allograft caused by IgG3? Targeting the PLA2 receptor. J Am Soc Nephrol 2012;23:1949-54.

How to cite this article: Gowda KK, Joshi K, Ramachandran R, Nada R. Monoclonal gammopathy associated membranous glomerulonephritis: A rare entity. Indian J Nephrol 2015;25:50-3.

Source of Support: Nil, **Conflict of Interest:** None declared.